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10/588,392	08/03/2006	Laszlo Takacs	NU-BI-659XX	8285

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	PAPER NUMBER
1639	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,392	TAKACS ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *3,4,7-16,19,20 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,17,18,21-23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Applicants' election with traverse of the elected species in the reply filed on February 17, 2009, is acknowledged. The traversal is on the grounds that there would not be an undue burden to search more than one species. This is not found persuasive because the art related to one species would not necessarily be relate to another species, such as the "complex analytes" in claims 6-16.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-26 are pending in the instant application; claims 3, 4, 7-16, 19, 20 and 24, are withdrawn; claims 1, 2, 5, 6, 17, 18, 21-23, 25 and 26 are the subject of the Office Action below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 5, 6, 17, 18, 21-23, 25 and 26, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, and all dependent claims, as well as claims 23, 25 and 26, are indefinite for reciting the term "using" in the second step of the claim because it is not clear what specific "use" is being carried out. For example, it is not clear if the term "using" means that the complex analyte is introduced to a host and then spleen cells are recovered for selecting the antibodies, or if there is another "use" that Applicants take advantage of in arriving at the monoclonal antibodies.

Claim 17 is indefinite for reciting the phrase "wherein said complex analyte is enriched in a class of analyte elements that share physicochemical properties" because one of ordinary skill in the art would not reasonably be able to determine the metes and bounds of this limitation. It is not clear if Applicants are intending to purify the complex analyte, or if Applicants instead are adding additional components to the complex analyte, or some other process step.

Claims 22 and 23 are indefinite for reciting the phrase "deploying a systems biology strategy for prioritization of said plurality of biomarkers for future development" because one of ordinary skill could not reasonably determine the metes and bounds of this limitation. The specification provides a definition, however, the definition itself is indefinite (see paragraphs 0014 and 0053). Furthermore, the "future development" limitation is an intended use limitation, and therefore has no patentable weight in the instant method.

Claim 26 is indefinite for reciting the phrase "prioritizing development of said individual biomarkers" because one of ordinary skill in the art could not reasonably determine the metes and bounds of this limitation. First, it is not clear if individual biomarkers have a "development". Second, it is not clear how these prioritizations are carried out or what it means to "prioritize developments".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, are obvious in view of Hoogenboom, Andersen, Nagai, Anderson and Burton:

Claim 1, 5, 6, 17, 21 25 and 26, are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hoogenboom *et al.*, *Immunotechnology*, *4*:1-20 (**1998**); in view of Andersen *et*

al., *PNAS*, *93*:1820-1824 (**1996**); Nagai *et al.*, *Biochemical Society Transactions, 31(part 6)*:1438-1440 (**2003**); and Anderson, U.S. Patent No. 6,887,687, issued on May 3, 2005, and/or Burton *et al.*, U.S. Patent No. 5,652,138, issued on July 29, 1997.

The claimed invention is generally directed towards a first step of generating a monoclonal antibody library from a complex analyte, followed by subtractive or differential screening.

Specifically, Claim 1 is directed towards a method of biomarker discovery, said method comprising the steps of:

providing a complex analyte as a candidate biomarker source; providing a control sample for said complex analyte;

using an aliquot of said complex analyte as an immunogen to generate a population of monoclonal antibodies directed against antigens in said complex analyte (note: this step of "using" is broad and does not require a specific approach to making the library such as a hybridoma, only that an antigen was initially used);

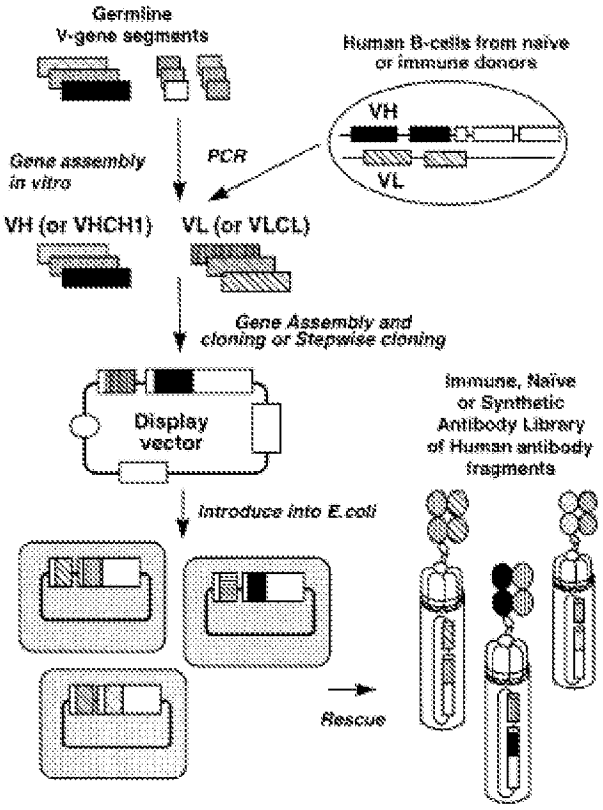
screening said population of monoclonal antibodies directed against antigens in said complex analyte against another aliquot of said complex analyte; screening said population of monoclonal antibodies directed against antigens in said complex analyte against an aliquot of said control sample; and

selecting at least one monoclonal antibody that exhibits a significant difference in binding to an antigen in said complex analyte compared to an antigen in said control sample, whereby the antigens selectively bound by said at least one selected monoclonal antibody are said biomarkers.

Hoogenboom provides an in-depth review article that relates to the use of antibody-based phage display methods. Certain of these methods include the production of monoclonal antibodies using phage display:

> "One of the most successful applications of phage display has been the isolation of monoclonal antibodies from large phage antibody libraries (Fig. 3). We will discuss the three types of such phage libraries, immune, naive and synthetic antibody libraries."

Hoogenboom, page 4, col. 2, lines 5-10. See also the entire discussion in the section titled, Antibody libraries, beginning on page 4 through page 8. Hoogenboom illustrates the above captioned process as follows:



Hoogenboom, Figure 3, page 5, col. 1.

As in step 3 of claim 1, Hoogenboom also teaches certain methods for preparing a host of antibodies from a response to a complex antigens (page 10, section titled, *Selection on complex antigens*). Hoogenboom also teaches subtractive methods for selecting antibodies (i.e., differential screening), wherein a control sample and another antigen sample are compared, such as normal cells vs. diseased cells (page 12, section titled, *Selection on cells*; see also Figure 4F on page 9, and description thereof; see also section titled, *Finding new antigens with phage antibody libraries*, on page 13). As in claim 21, the identity of the biomarker is determined (page 14, col. 1)

Although Hoogenboom teaches the *use* of a complex antigen, and references at least two sources for such an approach (see page 8, col. 2), he does not explicitly detail how to obtain at

least a first version of a monoclonal antibody for preparing a library, or a first monoclonal antibody library.

Andersen is directed towards the production of a recombinant antibody library from a complex antigen, wherein a host of antibodies are produced from the in vivo introduction of a complex antigen, and improved with phage display of Fab fragments. As in claim 5, the complex analyte of Andersen is fractionated; and as in claim 17 that the complex analyte is purified from other cell components (page 1820, section titled, *MHC Purification*). As in claim 6, Andersen teaches that the use of the complex antigen for generating the antibodies would have clinical use (see page 1824, col. 1, last paragraph).

Nagai teaches a method for preparing a library of monoclonal antibodies and its use for differentiating between cell types and control cells as well as cellular functions related to the display of the antigens that the antibody library is directed (see pages 1439-1440). Nagai also teaches identifying the biomarker (see page 1440).

Anderson is directed towards a new peptides in the human ataxin-1-like polypeptide family, methods of making such peptides, and methods of use. Anderson also teaches the importance of generating antibodies to such polypeptides, such as use as markers and potential therapeutic agents. Anderson teaches that antibody production, such as the engineering of monoclonal antibodies can be prepared using a number of well-established techniques (paragraph bridging cols. 28 and 29).

Burton is directed towards human monoclonal antibodies which immunoreact with and neutralize human immunodeficiency virus (HIV). Also disclosed are immunotherapeutic and diagnostic methods of using the monoclonal antibodies, as well as cell line for producing the monoclonal antibodies. Burton teaches that monoclonal antibodies can be the basis of a library that are prepare with recombinant techniques:

> "As shown by the present teachings and using the combinatorial library shuffling and screening methods, one can identify new heavy and light chain pairs that function as a HIV-neutralizing monoclonal antibody. In particular, one can shuffle a known heavy chain, derived from an HIV-neutralizing human monoclonal antibody, with a library of light chains to identify new H:L pairs that form a functional antibody according to the present invention. Similarly, one can shuffle a known light chain, derived from an HIV-neutralizing human monoclonal antibody, with a library of

> heavy chains to identify new H:L pairs that form a functional antibody according to the present invention."

Burton, paragraph bridging cols. 14 and 15.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the references is directed toward the use of highly selective antibodies for identifying and/or investigating antigens. Furthermore, one of ordinary skill in the art would have understood the advantages of using a monoclonal antibody as starting point for a complex analyte, followed by combinatorial approaches for mutation and affinity maturation as a means to produce a first library of monoclonal antibodies, and used the library with the method of Hoogenboom for differential expression screening, such as between healthy and diseased cells. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Claims 1, 2, 5, 6, 17, 18, 21, 25 and 26 are further obvious over McKeon and Zhang:

Claims 1, 2, 5, 6, 17, 18, 21, 25 and 26, are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoogenboom, Andersen, Nagai, Anderson and Burton, as applied to claims 1, 5, 6, 17, 21, 25 and 26 above, and further in view of McKeon *et al.*, U.S. Patent No. 7,396,905, issued on July 8, 2008, and Zhang, U.S. Patent Application Publication No. 2005/0009118 A1, published on January 13, 2005.

The limitations of claims 1, 5, 6, 17, 21, 25 and 26, and the corresponding teachings in the art are found in the rejection above, and are hereby incorporated into the instant rejection, however, the cited art does not explicitly teach the limitations of claims 2 and 18.

McKeon teaches that a plurality of monoclonal antibodies are used to identify a plurality of thymocyte markers, wherein certain markers are over expressed in unhealthy tissue (see section titled, Differentiation Analysis of T and B Cells in Csp1 and Csp2 Knock-Out Mice).

Zhang teaches differential profiling with antibodies specific towards certain markers:

> "As noted above, two different samples are usually used in the subject methods. In most embodiments, the two samples are pair of samples consisting of an "experimental" sample, i.e., a sample of interest, and a "control" sample to which the experimental sample may be compared. In many embodiments, therefore, the subject samples are pairs of cell types

> or fraction thereof, one cell type being a cell type of interest, e.g., abnormal cells, and the other a control, e.g., normal, cell type. If two fractions of cells are compared, the fractions are usually the same fraction from each of the two cells. In certain embodiments, however, two fractions of the same cell may be compared. Exemplary cell type pairs include, for example, cells isolated from a tissue biopsy (e.g., from a tissue having a disease such as colon, breast, prostate, lung, skin cancer, or infected with a pathogen etc.) and normal cells from the same tissue, usually from the same patient; cells grown in tissue culture that are immortal (e.g., cells with a proliferative mutation or an immortalizing transgene), infected with a pathogen, or treated (e.g., with environmental or chemical agents such as peptides, hormones, altered temperature, growth condition, physical stress, cellular transformation, etc), and a normal cell (e.g., a cell that is otherwise identical to the experimental cell except that it is not immortal, infected, or treated, etc.); a cell isolated from a mammal with a cancer, a disease, a geriatric mammal, or a mammal exposed to a condition, and a cell from a mammal of the same species, preferably from the same family, that is healthy or young; and differentiated cells and non-differentiated cells from the same mammal (e.g., one cell being the progenitor of the other in a mammal, for example). In one embodiment, cells of different type, e.g., neuronal and non-neuronal cells, or cells of different status (e.g. before and after a stimulus on the cells) may be used. In another embodiment of the invention, the experimental material is cells susceptible to infection by a pathogen such as a virus, e.g. human immunodeficiency virus (HIV), etc., and the control material is cells resistant to infection by the pathogen. In another embodiment of the invention, the sample pair is represented by undifferentiated cells, e.g., stem cells, and differentiated cells."

Zhang, paragraph 0055.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of the references are directed towards the use of antibodies as diagnostics. One of ordinary skill in the art would have recognized the advantages of using a population of antibodies as in McKeon for distinguishing certain cells as diseased from the higher affinity of a particular antibody that is higher than that of a control or healthy tissue. Therefore, the invention as a whole was *prima facie* obvious at the time it was invented.

Common Ownership of Claimed Invention Presumed

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Conclusions

No claim is allowable

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey S. Lundgren/
Patent Examiner, Art Unit 1639